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Adverse immunologic effects of antithyroid drugs

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Propylthiouracil and methimazole are frequently used in the management of hyperthyroidism. Two patients in whom adverse immunologic effects other than isolated agranulocytosis developed during treatment with propylthiouracil are described. A review of the literature revealed 53 similar cases over a 35-year period. Rash, fever, arthralgias and granulocytopenia were the most common manifestations. Vasculitis, particularly with cutaneous manifestations, occurs and may be fatal. The clinical evidence suggests that an immunologic mechanism is involved. A number of different autoantibodies were reported, but antinuclear antibodies were infrequent, and none of the cases met the criteria for a diagnosis of systemic lupus erythematosus. Thus, the reactions do not represent a true drug-induced lupus syndrome. Current hypotheses and experimental data regarding the cause of the reactions are reviewed. No specific clinical subgroup at high risk can be identified, and manifestations may occur at any dosage and at any time during therapy. Cross-reactivity between the two antithyroid drugs can be expected. Except for minor symptoms (e.g., mild arthralgias or transient rash), such reactions are an indication for withdrawal of the drug and the use of alternative methods to control the hyperthyroidism. In rare cases of severe vasculitis a short course of high-dose glucocorticoid therapy may be helpful.

On utilise souvent le propylthiouracile et le méthimazole dans le traitement de l'hyperthyroïdie. Présentation de deux malades ayant accusé lors d'un traitement au propylthiouracile des effets immunologiques autres qu'une agranulocytose isolée. Une recherche bibliographique décèle 53 cas comparables répartis sur 35 ans. Les symptômes les plus fréquents sont les éruptions, la fièvre, l'arthralgie et la granulocytopénie. La vasculite survient surtout en présence d'une éruption; elle est parfois mortelle. Le tout fait penser à un trouble immunologique. En dépit de la démonstration de divers auto-anticorps, on trouve rarement des anticorps antinucléaires; aucun de ces cas ne satisfait les critères du diagnostic d'un lupus érythémateux disséminé. Aussi ne saurait-on parler ici d'un syndrome lupoïde médicamenteux. Les auteurs passent en revue les hypothèses actuelles et les données expérimentales pertinentes à la cause de ces réactions. On ne peut définir, parmi les hyperthyroïdiens, un sous-groupe prédisposé aux effets décrits ici; ceux-ci peuvent survenir quelle que soit la posologie et à tout moment du traitement. On doit s'attendre à une réactivité croisée à l'égard des deux médicaments susdits. Hormis les symptômes légers (telles une petite arthralgie ou une éruption fugace), les phénomènes décrits ci-dessus indiquent l'arrêt du médicament et le recours à un autre mode de traitement de l'hyperthyroïdie. Rarement, en présence d'une vasculite grave, on se trouvera bien d'une courte corticothérapie à fortes doses.

Propylthiouracil and methimazole are thioureylene derivatives commonly used in the management of hyperthyroidism, especially that due to Graves' disease.[1] These drugs are used for control of the hyperthyroid state until spontaneous remission occurs or the effects of radioiodine therapy take place or in the preparation of the patient for thyroidectomy. Since hyperthyroidism is a common endocrine problem and no alternative drug therapy is available, these drugs will continue to be used frequently by physicians caring for these patients.

Recently we observed adverse immunologic effects in two patients receiving propylthiouracil. A search of the literature for such cases revealed that similar adverse effects have been reported inter-

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mittently during the 35 years that these antithyroid drugs have been available. In this paper we briefly describe our patients and review the nature and frequency of the various adverse effects reported as well as current hypotheses as to their cause. Since isolated agranulocytosis is a well-known adverse effect of thioureylene drug therapy and has previously been reviewed,[1] we emphasize other adverse immunologic effects that are not as well known.

Illustrative cases

Case 1

A 47-year-old woman was treated for Graves' disease in 1963 with propylthiouracil and radioiodine. She was well until June 1983, when she presented with recurrent symptoms. Her thyroid hormone levels confirmed the diagnosis of recurrent hyperthyroidism, and a thyroid scan showed diffusely increased uptake of tracer radioactive iodine. Radioiodine was administered and therapy with propylthiouracil restarted.

Four weeks later the patient returned with a 3-week history of intermittent fever, chills, nausea, vomiting, anorexia and tremulousness. She had a temperature of 40°C, no palpable thyroid tissue, mild splenomegaly and a purpuric rash over her buttocks and lower extremities. The serum triiodothyronine level and free thyroxine index were 0.8 (normally 1.5 to 3.4) nmol/L and 17 (normally 51 to 167) respectively. Antithyroglobulin and antimicrosomal antibodies were present. There was mild anemia but no reticulocytosis or spherocytosis. The direct antiglobulin test gave positive results for both IgG and C3. The leukocyte count was 0.7 (normally 4.0 to 11.0) $\times 10^9$/L, with only 0.4 $\times 10^9$/L neutrophils. The platelet count was 122 (normally 140 to 440) $\times 10^9$/L. The partial thromboplastin time was elevated, at 63 (control value 32) seconds, and the prothrombin time slightly elevated, at 13.1 (control value 11.2) seconds. Serum levels of electrolytes, measured urea, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase and bilirubin were normal. An assay for antinuclear antibodies gave negative results. Serum protein electrophoresis showed slight hypergammaglobulinemia (γ-globulin level 19 [normally 9 to 18] g/L), with elevation of the IgG fraction. The C4 level was 0.1 (normally 0.2 to 0.5) g/L. Urinalysis gave normal results. A skin biopsy specimen showed minute perivascular lymphocytic infiltrates in the upper dermis, with intact vessel walls.

Propylthiouracil therapy was stopped, and hydrocortisone, 250 mg given intravenously every 6 hours, administered. The symptoms dissipated over a few days, and the hematologic abnormalities, rash and splenomegaly resolved over the next 2 weeks. Corticosteroid therapy was rapidly tapered off, and the patient has remained well and become euthyroid without further therapy.

Case 2

A 31-year-old woman was first seen at our institution in December 1981. Graves' disease had previously been diagnosed on the basis of a diffuse goitre and abnormal thyroid indices. Propylthiouracil had been prescribed, but the patient had stopped taking it. At the time of referral she was still mildly symptomatic and had an elevated serum triiodothyronine level (4.3 nmol/L). Therapy with propylthiouracil, 100 mg taken orally three times daily, was restarted, with subsequent improvement.

The patient was well until October 1982, when arthralgias of the elbows, knees and ankles developed, along with an erythematous maculopapular rash on her forehead. Propylthiouracil therapy was stopped. The rash resolved promptly, and the arthralgias resolved over the next month. The patient has remained euthyroid and well.

Nature and frequency of adverse effects

Our two cases demonstrate different hypersensitivity reactions to propylthiouracil. In patient 1 the prominent manifestations were fever, leukopenia, purpuric rash and splenomegaly, whereas patient 2 had migratory arthralgias and an erythematous rash. A review of the literature revealed that over a 35-year period 53 cases of adverse immunologic effects associated with antithyroid drugs were reported. The reactions occurred at any age. As expected, given that hyperthyroidism is predominant in females, more females than males were affected. Toxic effects occurred at any dosage, at the first or repeated exposure to the drug and at any duration of therapy, from days[3] to several years.[4-6]

The four most frequently reported manifestations were rash, fever, joint symptoms and granulocytopenia (Table I). Rash, seen in 50% of cases, was generally purpuric or, less frequently, ulcerative. Skin biopsy, when performed, often revealed vasculitis.[5,7-12] Fever, reported in almost 50% of cases, was rarely associated with infection despite the often associated leukopenia, which indicates that it is a manifestation of hypersensitivity. Joint symptoms occurred in 40% and most often consisted of symmetric involvement of distal joints; half of these patients had evidence of synovitis.

Granulocytopenia, a well-recognized adverse effect of thioureylene therapy with an incidence rate in exposed patients of about 4%,[2] occurred in 45% of these cases. However, since in some cases it was the only symptom, it may not be a manifestation of hypersensitivity but, rather, a direct toxic effect.[2] The fact that antithyroid drugs are actively concentrated by granulocytes is also compatible with this hypothesis.[2,6] Agranulocytosis (granulocyte count less than 0.25 $\times 10^9$/L) occurs in only 0.3% of treated patients.[2] This is an idiosyncratic reaction of rapid and unpredictable onset, distinct from the more common asymptomatic granulocy-

topenia. In some cases antineutrophil antibodies have been identified.[13,27-29] Furthermore, in some patients with agranulocytosis, lymphocyte transformation was induced by exposure of the lymphocytes in culture to autologous serum with antithyroid drugs.[29] A search for such antibodies in patients with benign granulocytopenia has not been carried out, and therefore it is not possible to state with certainty that benign granulocytopenia is secondary to direct drug toxicity. Aplastic anemia has been associated with methimazole therapy,[30,31] and in one report an inhibitor to colony-forming units in culture was found in the patient's serum.[31]

Other reported laboratory abnormalities include anemia, thrombocytopenia and polyclonal hypergammaglobulinemia. Many cases of anemia were not fully investigated. In our patient 1 anemia was associated with a positive result of a direct antiglobulin test. Although there was no specific evidence of hemolysis in our patient, this manifestation has been described.[14] In one case of thrombocytopenia the patient was found to have platelet-associated IgG and many megakaryocytes in the bone marrow, findings indicative of immune-destructive thrombocytopenia.[13] The hypergammaglobulinemia found in our patient 1 and reported by others may reflect production of nonspecific, drug-stimulated polyclonal antibodies. Interestingly, there have been cases of development of autoantibodies to marrow precursor cells,[31] insulin[32,33] or glucagon[34] during methimazole therapy. Circulating immune complexes were demonstrated in a few cases,[9,16] but their significance is uncertain, as such complexes have been described in untreated thyroid disease.[35,36]

Vasculitic involvement of organs other than the skin was uncommon. However, a fatal case of periarteritis[37] and cases of nephritis,[5,9,17] myositis[9] and cavitary pulmonary infiltrates[6] have been reported.

Hepatitis has also been observed as a complication of antithyroid drug therapy.[16,18,38-43] In some cases it was the only finding and therefore, as in cases of granulocytopenia, may be a direct toxic effect of the drug or its metabolites. However, in two cases hepatitis developed in conjunction with other systemic manifestations.[16,18] In one of these[18] and in a case of isolated hepatitis,[42] lymphocyte sensitization to propylthiouracil was demonstrated, which suggests an immunologic mechanism.

Hypoprothrombinemia, which occurred in our patient 1, has been reported in the absence of other evidence of liver dysfunction.[7,9,20,44,45] There have been no reports of circulating anticoagulants. The cause of the possible factor deficiency is unknown.

In several cases there was only one manifestation, which, given the clinical or laboratory evidence, was probably immunologically mediated. These included aplastic anemia,[31] antibodies to insulin,[32,33] antibodies to glucagon,[34] periarteritis,[37] polyarthritis,[24] leukopenia[27-29] and hepatitis.[42]

Most of the toxic effects ascribed to antithy-

Table I — Reported adverse immunologic effects of antithyroid drugs

Drug, patient's age, sex	Dosage, mg/d	Fever	Rash	Arthralgia	Arthritis	Splenomegaly	Granulocytopenia	Agranulocytosis*	Anemia	Thrombocytopenia	Antinuclear antibody	Hypergammaglobulinemia	Hepatitis
Propylthiouracil													
37, M[3]	400 × 5 d		•	•							•		
18, F[4]	50–100 × 5 yr	•	•	•		•	•					•	
9, F[5]	300–600 × 18 mo		•						•		•		
13, F[6]	300 × 3 yr	•	•						•				
26, F[6]	Sporadic	•	•						•				
46, F[7]	400 × 2 wk	•	•				•						
36, F[8]	400 × 3 yr		•		•		•		•		•		
14, F[9]	400 × 1.5 yr	•	•	•		•	•		•	•			
31, F[10]	400 × 4 yr	•	•	•		•	•		•				
27, F[11]	? × 4 d		•	•			•						
37, F[11]	300 × ? mo		•		•							•	
13, F[12]	250 × 2 yr		•	•			•						
41, F[13]	100 × 1.5 yr		•	•			•					•	
62, F[13]	100 × 3 yr		•				•					•	
15, F[13]	225 × 15 mo	•	•			•		•	•	•	•	•	
7, F[14]	200 × 1.5 yr		•			•	•		•		•		
50, M[15]	150 × 2 mo	•	•							•			
23, F[16]	300 × 6 d	•	•			•							•
13, M[17]	300 × 6 mo	•		•			•		•		•	•	
47, F[18]	600 × ? mo	•	•				•						•
25, F[19]	300 × 6 wk			•								•	
16, F[20]	75–150 × 2 yr		•			•					•	•	
27, F[21]	150 × 2 yr	•			•		•					•	
12, F[22]	150 × 22 mo		•		•						•		
13, F[22]	200 × 1.5 yr		•		•						•		
47, F[22]	400 × ? mo	•			•							•	
Methimazole													
69, M[3]	30–60 × 2 wk		•	•									
23, F[4]	45 × 2 wk				•						•		
28, F[5]	30 × 3 wk	•	•		•								
63, F[23]	30 × 2 wk				•							•	
15, F[24]	60 × 3 wk	•	•		•								
26, F[25]	60 × 1.5 yr	•			•								

*Defined as leukocyte count less than 1.0×10^9/L or granulocyte count less than 0.25×10^9/L.

roid drugs are felt on clinical grounds to be immunologically mediated; in some cases there was also supportive laboratory evidence of abnormal humoral or cellular immunologic activity. Many of the reactions to propylthiouracil were considered to be a lupus-like syndrome. However, there must be adequate criteria for a true diagnosis of drug-induced systemic lupus erythematosus (SLE).[46] Although antinuclear antibodies were present in a few cases (10 of 53), none of the cases had adequate criteria for the diagnosis of SLE.[47] Also, the incidence of antinuclear antibodies in a propylthiouracil-treated patient population was reported to be no greater than that in a control population.[48] In contrast to these findings are the SLE-like syndromes associated with hydralazine hydrochloride and procainamide, in which antinuclear antibodies are present in all patients and in a large number of asymptomatic patients exposed to the drug.[49] Thus, it is more appropriate to refer to the side effects of antithyroid drugs as immunologically mediated than as lupus-like syndromes.

The reactions were characterized by symptoms and signs that varied widely in severity, ranging from rash and arthralgia (frequently seen) to agranulocytosis and fatal vasculitis (rare). Potentially life-threatening manifestations were not heralded by prodromes of milder symptoms and are therefore not predictable. Therapy with the drug was stopped in most cases when the toxic effects appeared. Rechallenge was not described; it occurred inadvertently in one case and resulted in death.[37] However, in several cases milder reactions (e.g., rash and joint symptoms) resolved despite continued administration of the drug.[17]

Cross-reactivity between antithyroid drugs

Several patients reacted to both propylthiouracil and methimazole when given a trial of each.[7,16,19,24,50] A recent study showed that in some patients with propylthiouracil-induced agranulocytosis, peripheral blood lymphocytes underwent transformation in the presence of methimazole or carbimazole.[29] As well, serum from some of these patients induced neutrophil agglutination in the presence of thionamide drugs other than propylthiouracil. The observations of both clinical and in-vitro cross-reactivity among these drugs strengthen the hypothesis that the adverse effects are immunologically mediated.

Cause of adverse effects

The mechanism of stimulation of antibody production and of cellular immunity remains unclear. The stimulation of immune responses to various unrelated autoantigens by antithyroid drugs is in contrast to the suggested immunosuppressive activities of these drugs.[51-53] Propylthiouracil has been shown in vitro to suppress lectin-induced incorporation of tritiated thymidine into the DNA of peripheral blood lymphocytes.[51] In vivo, carbimazole has been associated with decreased levels of antimicrosomal antibodies and of antibodies to the receptor for thyroid-stimulating hormone.[54] The suppressor activity of peripheral blood lymphocytes in patients with Graves' disease, which is diminished, has been shown to revert toward normal during antithyroid drug therapy.[55] However, similar findings have been reported in patients treated with radioiodine,[56] which suggests that the hyperthyroid state itself may be responsible for the immunologic abnormalities.[55]

The aberrant immune responses described in this review may be related to the underlying abnormal immunologic function of patients with Graves' disease. However, there was an insufficient number of cases and insufficient detail to determine whether the risk of drug hypersensitivity differed in hyperthyroidism due to causes other than Graves' disease. The mechanism by which the drugs stimulate the response may involve the thiol group of the drugs, which permits covalent bonding to cellular macromolecules. Such a complex with thyroglobulin has been demonstrated.[36] The drug may therefore serve as a hapten and induce antibody production. Such a mechanism may give rise to single autoantibodies (to insulin, glucagon, neutrophils or marrow precursor cells). However, when multiple autoantigens are targeted in a given patient, drug modification of multiple macromolecules or of proteins involved in regulation of the immune response would have to be postulated.

Alternatively, metabolites of propylthiouracil may compete with thymidine triphosphate as a substrate and therefore inhibit synthesis of DNA.[51] If the metabolite is incorporated into DNA, abnormalities of regulation of immune function may occur that ultimately result in the expression of adverse effects.[51]

It is not clear why certain people are susceptible to these adverse effects. Similarly, the manifestation of toxicity in different organ systems indicates heterogeneity of response. Genetic deficiencies of drug-metabolizing enzymes have been demonstrated by Spielberg[57] in patients with adverse reactions to acetaminophen and anticonvulsant drugs. It is not known whether such deficiencies are involved in adverse effects of antithyroid drugs. Further investigation of the metabolism of antithyroid drugs[58] and of the associated immunologic abnormalities should provide insight into this problem.

Guidelines for management

Despite uncertainty as to the pathogenesis of the adverse effects, review of the literature does provide guidelines to the clinician for the management of these patients. First, the reactions are unpredictable and occur at any age, dose and duration of therapy. Cooper and colleagues[59] studied a series of patients with antithyroid drug-

induced agranulocytosis and suggested that older patients and those receiving high doses of methimazole are at greatest risk. However, when other reactions are considered, such trends are not apparent. Therefore, awareness of the entity is necessary for its early recognition. Routine monitoring of laboratory values is not helpful. Patients should be instructed to immediately report the classic presenting symptoms: fever, sore throat, rash and arthralgias. Since rash or arthralgias without other systemic manifestations may resolve spontaneously, continued therapy with close observation is possible in such cases. However, if these symptoms persist or if more serious manifestations occur, therapy should be stopped immediately. Withdrawal of the drug is usually adequate to reverse the toxic effects.

The benefit of corticosteroid therapy is uncertain, but this treatment is recommended in cases of life-threatening or poorly resolving toxic effects. We suggest high-dose therapy (1 mg/kg of prednisone or an equivalent drug) for the former situation and more moderate dosages (0.5 mg/kg) for the latter. These drugs should be rapidly tapered off once the toxic effects have resolved. In the presence of agranulocytosis and fever without an evident infectious source, broad-spectrum antibiotic therapy would be appropriate until the granulocyte count reaches 1.0×10^9/L.

Because of cross-reactivity, therapy with another thionamide drug is not advisable, and alternative forms of management of the hyperthyroidism should be instituted.

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References

1. Solomon DH. Antithyroid drugs. In Werner SC, Ingbar SH (eds): *The Thyroid, a Fundamental and Clinical Text.* 4th ed. Har-Row, New York, 1978: 814-821
2. Rosove MH: Agranulocytosis and antithyroid drugs. *West J Med* 1977; 126: 339-343
3. Searle RP, Plymate SR, Troup GM: Familial thionamide-induced lupus syndrome in thyrotoxicosis. *J Rheumatol* 1981; 8: 498-500
4. Walzer RA, Einbinder J: Immunoleukopenia as an aspect of hypersensitivity to propylthiouracil. *JAMA* 1963; 184: 743-746
5. Cassorla FG, Finegold DN, Parks JS et al: Vasculitis, pulmonary cavitation, and anemia during antithyroid drug therapy. *Am J Dis Child* 1983; 137: 118-122
6. Houston BD, Crouch ME, Brick JE et al: Apparent vasculitis associated with propylthiouracil use. *Arthritis Rheum* 1979; 22: 925-928
7. Reidy TJ, Upshaw JD, Chesney T: Propylthiouracil-induced vasculitis: a fatal case. *South Med J* 1982; 75: 1297-1298
8. Oh BK, Overveid GPJM, MacFarlane ID: Polyarthritis induced by propylthiouracil. *Br J Rheumatol* 1983; 22: 106-108
9. Griswold WR, Mendoza SA, Johnston W et al: Vasculitis associated with propylthiouracil. *West J Med* 1978; 128: 543-546
10. Vasily DB, Tyler WB: Propylthiouracil-induced cutaneous vasculitis. *JAMA* 1980; 243: 458-461
11. Verdy M, Pretty H, Cadotte M et al: Vasculite secondaire aux antithyroidiens. *Union Med Can* 1975; 104: 576-579
12. Gammeltoft M, Kristensen JK: Propylthiouracil-induced cutaneous vasculitis. *Acta Derm Venereol (Stockh)* 1982; 62: 171-173
13. Berkman EM, Orlin JB, Wolfsdorf J: An anti-neutrophil antibody associated with propylthiouracil-induced lupus-like syndrome. *Transfusion* 1983; 23: 135-138
14. Breese TJ, Solomon IL: Granulocytopenia and hemolytic anemia as complications of propylthiouracil therapy. *J Pediatr* 1975; 86: 117-119
15. Fewell RA, Engel EF, Zimmerman SL: Acute thrombopenic purpura associated with administration of propylthiouracil. *JAMA* 1950; 143: 891-892
16. Takuwa N, Kojima I, Ogata E: Lupus-like syndrome — a rare complication in thionamide treatment for Graves' disease. *Endocrinol Jpn* 1981; 28: 663-667
17. Amrhein JA, Kenny FM, Ross D: Granulocytopenia, lupus-like syndrome, and other complications of propylthiouracil therapy. *J Pediatr* 1970; 76: 54-63
18. Pacini F, Sridama V, Refetoff S: Multiple complications of propylthiouracil treatment: granulocytopenia, eosinophilia, skin reaction and hepatitis with lymphocyte sensitization. *J Endocrinol Invest* 1982; 5: 403-407
19. Shabtai R, Shapiro MS, Orenstein D et al: The antithyroid arthritis syndrome reviewed. *Arthritis Rheum* 1984; 27: 227-229
20. Sammon TJ, Peden VH, Witzleben C et al: Disseminated intravascular coagulation complicating propylthiouracil therapy. *Clin Pediatr (Phila)* 1971; 10: 739-742
21. Wing ES, Asper SP: Propylthiouracil in hyperthyroidism. *Bull Johns Hopkins Hosp* 1952; 90: 201-227
22. Hung W, August GP: A "collagen-like" syndrome associated with antithyroid therapy. *J Pediatr* 1973; 82: 852-854
23. Farbman K, Wheeler MF, Glick SM: Arthritis induced by antithyroid medication. *NY State J Med* 1969; 69: 826-831
24. Librik L, Sussman L, Bejar R et al: Thyrotoxicosis and collagen-like disease in three sisters of American Indian extraction. *J Pediatr* 1970; 76: 64-68
25. Kurtz MD: Migratory polyarthritis occurring with methimazole therapy. *NY State J Med* 1968; 68: 2810-2811
26. Lam DCC, Lindsay RH: Accumulation of 2-[^{14}C] propylthiouracil in human polymorphonuclear leukocytes. *Biochem Pharmacol* 1979; 28: 2289-2296
27. Bilezikian SB, Laleli Y, Tsan MF et al: Immunological reactions involving leukocytes: 3. Agranulocytosis induced by antithyroid drugs. *Johns Hopkins Med J* 1976; 138: 124-129
28. Weitzman SA, Stossel TP: Drug-induced immunological neutropenia. *Lancet* 1978; 1: 1068-1072
29. Wall JR, Fang SL, Kuroki T et al: In vitro immunoreactivity to propylthiouracil, methimazole, and carbimazole in patients with Graves' disease: a possible cause of antithyroid drug induced agranulocytosis. *J Clin Endocrinol Metab* 1984; 58: 868-872
30. Edell SL, Bartuska DG: Aplastic anemia secondary to methimazole — case report and review of hematologic side effects. *J Am Med Wom Assoc* 1975; 30: 412-413
31. Moreb J, Shemesh O, Shilo S et al: Transient methimazole-induced bone marrow aplasia: in vitro evidence for a humoral mechanism of bone marrow suppression. *Acta Haematol (Basel)* 1983; 69: 127-131
32. Benson EA, Ho P, Wang C et al: Insulin autoimmunity as a cause of hypoglycemia. *Arch Intern Med* 1984; 144: 2351-2354
33. Hirata Y: Methimazole and insulin autoimmune syndrome with hypoglycemia. *Lancet* 1983; 2: 1037-1038
34. Sanke T, Kondo M, Moriyama Y et al: Glucagon binding autoantibodies in a patient with hyperthyroidism treated with methimazole. *J Clin Endocrinol Metab* 1983; 57: 1140-1144
35. Calder EA, Penhale WJ, Barnes EW et al: Evidence for circulating immune complexes in thyroid disease. *Br Med J* 1974; 2: 30-31

36. Bronee D, Delespesse G, Debisschop MJ et al: Circulating immune complexes in various thyroid diseases. *Clin Exp Immunol* 1979; 36: 379-383
37. McCormick RV: Periarteritis occurring during propylthiouracil therapy. *JAMA* 1950; 144: 1453-1454
38. Martinez-Lopez JI, Greenberg SE, Kling RR: Drug-induced hepatic injury during methimazole therapy. *Gastroenterology* 1962; 43: 84-87
39. Livingston HJ, Livingston SF: Agranulocytosis and hepatocellular jaundice. *JAMA* 1947; 135: 422-425
40. Parker LN: Hepatitis and propylthiouracil. *Ann Intern Med* 1975; 82: 228-229
41. Fedotin MS, Lefer LG: Liver disease caused by propylthiouracil. *Arch Intern Med* 1975; 135: 319-321
42. Mihas AA, Holley P, Koff RS et al: Fulminant hepatitis and lymphocyte sensitization due to propylthiouracil. *Gastroenterology* 1976; 70: 770-774
43. Reddy CM: Propylthiouracil and hepatitis: a case report. *J Natl Med Assoc* 1979; 71: 1185-1186
44. Craddock CG, Shotton D, Crockett CL et al: Severe hypoprothrombinemia following propylthiouracil treatment of thyrotoxicosis. *N Engl J Med* 1951; 244: 549-551
45. Greenstein RH: Hypoprothrombinemia due to propylthiouracil therapy. *JAMA* 1960; 173: 1014-1015
46. Tam EM, Cohen AS, Fries JF et al: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-1277
47. Hess EV: Introduction to drug-related lupus. *Arthritis Rheum* 1981; 24 (8): vi-ix
48. Cetina JA, Fishbein E, Alarcon-Segovia D: Antinuclear antibodies and propylthiouracil therapy. *JAMA* 1972; 220: 1012
49. Harmon CE, Portanova JP: Drug-induced lupus: clinical and serological studies. *Clin Rheum Dis* 1982; 8: 121-135
50. Chen B, Lang R, Jurrin Y et al: Recurrent agranulocytosis induced by two different antithyroid agents. *Med J Aust* 1983; 2: 38-39
51. Wall JR, Manwar GL, Greenwood DM et al: The in vitro suppression of lectin induced ^{3}H-thymidine incorporation into DNA of peripheral blood lymphocytes after the addition of propylthiouracil. *J Clin Endocrinol Metab* 1976; 43: 1406-1409
52. McGregor AM, Peterson MM, McLachlan SM et al: Carbimazole and the autoimmune response in Graves' disease. *N Engl J Med* 1980; 303: 302-307
53. Goldrath N, Shoham J, Bank H et al: Antithyroid drugs and lymphocyte function: 2. The in vivo effect of blastogenesis and suppressor cell activity in Graves' disease. *Clin Exp Immunol* 1982; 50: 62-69
54. Chan JYC, Walfish PG: Activated (Ia+) T-lymphocytes and their subsets in autoimmune thyroid disease: analysis by dual laser flow microfluorocytometry. *J Clin Endocrinol Metab* 1986; 62: 403-409
55. Volpé R: Autoimmune thyroid disease. In Volpé R (ed): *Autoimmunity and Endocrine Disease*, Dekker, New York, 1985: 109-285
56. Papapetrou PD, Mothon S, Alexander WD: Binding of the ^{35}S of ^{35}S-propylthiouracil by follicular thyroglobulin in vivo and in vitro. *Acta Endocrinol (Copenh)* 1975; 79: 248-258
57. Spielberg SP: In vitro assessment of pharmacogenetic susceptibility to toxic drug metabolites in humans. *Fed Proc* 1984; 43: 2308-2313
58. Kampmann JP, Hansen JM: Clinical pharmacokinetics of antithyroid drugs. *Clin Pharm* 1981; 6: 401-428
59. Cooper DS, Goldminz D, Levin AA et al: Agranulocytosis associated with antithyroid drugs. Effects of patient age and drug dose. *Ann Intern Med* 1983; 98: 26-29

[illegible] generally occurs during the first 4 weeks of therapy. It is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission [illegible] continued. Pruritus without rash occurs in about 2% of patients. Between 7 and 10% of patients with skin rash have shown an eosinophilia and/or positive ANA titers. A reversible [illegible] has been reported. **Allergic:** Angioedema of the face, mucous membranes of the mouth, or of the extremities has been observed in approximately 0.1% [illegible] of captopril therapy. Serum sickness and bronchospasm have been reported. One case of laryngeal edema has been reported. **Cardiovascular:** Hypotension may [illegible] (see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy). Tachycardia, chest pain, and palpitations have each been observed in approximately [illegible] of patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in 0.2 to 0.3% of patients. Flushing or pallor has been reported in 0.2 to 0.5% of patients. **Alterations in Taste:** 2% of patients receiving ≤ 150 mg/day of CAPOTEN developed a diminution or loss of taste perception. At doses > 150 mg per day 7% of patients experienced this effect. Taste impairment is [illegible] The following have been reported in about 0.5 to 2% of patients [illegible] **CNS.** [illegible] headache [illegible] fatigue, insomnia, paresthesia. **Others:** [illegible] dry eyes. **Altered Laboratory Findings:** Elevations of liver enzymes have been noted in a few patients but no [illegible] Rare cases of cholestatic jaundice, and of hepatocellular injury with or without secondary cholestasis, have been reported. Elevation of BUN and serum creatinine [illegible] In instances of reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may [illegible] resulting in transient rises in serum creatinine and BUN. Small increases in the serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION CAPOTEN (captopril) should be taken one hour before meals. DOSAGE MUST BE INDIVIDUALIZED. **Adults: Hypertension:** Initiation of therapy requires consideration of recent [illegible] drug treatment, the extent of blood pressure elevation, salt restriction, and other clinical circumstances. If possible, discontinue the patient's previous antihypertensive drug regimen for one week before starting CAPOTEN. The initial dose of CAPOTEN is 25 mg t.i.d. If satisfactory reduction of blood pressure has not been achieved after one or two weeks, the dose may be increased to 50 mg t.i.d. The dose of CAPOTEN [illegible] usually does not exceed 50 mg t.i.d. Therefore, if the blood pressure has not been satisfactorily controlled after 1 to 2 weeks at this dose (and the patient is not already receiving a diuretic), a modest [illegible] thiazide-type diuretic (e.g., hydrochlorothiazide, 25 mg daily) should be added. The diuretic dose may be increased at 1 to 2 week intervals until its highest usual antihypertensive dose is reached. In a patient [illegible] receiving a diuretic, CAPOTEN therapy should be initiated under close medical supervision (see WARNINGS and PRECAUTIONS [Drug Interactions] regarding hypotension), with dosage and titration of CAPOTEN as noted above. In severe hypertension, if further blood pressure reduction is required, the dose may be increased to 100 mg t.i.d., and then, if necessary, to 150 mg t.i.d., while continuing the diuretic. The usual dose range is 25 to 150 mg t.i.d. A maximum daily dose of 450 mg CAPOTEN should not be exceeded. For patients with accelerated or malignant hypertension, when temporary discontinuation of current antihypertensive [illegible] more normotensive blood pressure levels is indicated, diuretic should be continued but other concurrent antihypertensive medication should be stopped [illegible] When necessitated by the patient's clinical condition, the daily dose of CAPOTEN may be increased every 24 hours under [illegible] medical supervision until a satisfactory blood pressure response is obtained or the maximum dose is reached. In this regimen, addition of a more potent diuretic, e.g. furosemide, may also be indicated. Beta-blockers may also be used in conjunction with CAPOTEN therapy (see PRECAUTIONS - Drug Interactions) but the effects of the two drugs are less than additive. **Heart Failure:** Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. In patients with either normal or low blood pressure, who have been vigorously treated with diuretics and who may be hyponatremic and/or hypovolemic, a starting dose of 6.25 or 12.5 mg t.i.d. may minimize the magnitude or duration of the hypotensive effect (see WARNINGS [Hypotension]). For these patients, titration to the usual daily dosage [illegible] within the next several days. For most patients the usual initial daily dosage is 25 mg t.i.d. After a dose of 50 mg t.i.d. is reached, further increases in dosage should be delayed, where possible, for [illegible] two weeks to determine if a satisfactory response occurs. Most patients studied have had a satisfactory clinical improvement at 50 or 100 mg t.i.d. A maximum daily dose of 450 mg of CAPOTEN should not be exceeded. CAPOTEN is to be used in conjunction with a diuretic and digitalis. Therapy must be initiated under very close medical supervision. **Dosage Adjustment in Renal Impairment:** Because CAPOTEN is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady state captopril levels and will reach higher steady state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent [illegible] patients with significant renal impairment, initial daily dosage of CAPOTEN should be reduced, and [illegible] titration, which should be quite slow (1 to 2 week intervals). After the desired therapeutic [illegible] been achieved, the dose should be slowly back titrated to determine the minimal effective dose. When concomitant diuretic therapy is required, a loop diuretic (e.g. furosemide) rather than a thiazide diuretic is preferred in patients with [illegible] CAPOTEN is removed by hemodialysis. **AVAILABILITY** CAPOTEN (captopril) is available as tablets [illegible] CAPOTEN 25 [illegible] SQUIBB [illegible] **Storage:** Store at room temperature. Protect from moisture. [illegible] **Product monograph available to physicians upon request.**

The following table which is based on theoretical considerations may be useful as a guide to minimize drug accumulation.

Creatinine Clearance (mL/min/1.73 m²)	Dosage Interval (Hours)
> 75	8
75-35	12-24
34-20	24-48
19-8	48-72
7-5	72-108 (3 to 4.5 days)

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